REMARKS

Claims 1-10 and 16 are pending and stand rejected. Claims 11-15, 17, and 20-44 stand withdrawn as being drawn to non-elected inventions, and claims 18 and 19 stand withdrawn as being drawn to non-elected species.

Applicants have amended paragraphs beginning at pages 12, 21, 26-28, 30, and 34 of the specification to capitalize and define trademarks. With respect to the amendments to paragraphs beginning at page 30, Applicants note that the underlined portions of SEQ ID NOS:21 and 23 do not represent newly added text. Rather, the underlining within those sequences was present in the application as filed, and indicates the location of start codons.

Applicants have amended independent claim 1 to recite a purified polypeptide comprising an amino acid sequence selected from the group consisting of: (a) the amino acid sequence of SEQ ID NO:1, 3, or 36; (b) a sequence having at least seven contiguous residues of the amino acid sequence of SEQ ID NO:1; (c) a sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO:1; and (d) a sequence having at least 85% sequence identity to a fragment of SEQ ID NO:1 at least seven contiguous residues in length. Dependent claims 6-10 have been amended for consistency with amended claim 1. In addition, claims 2-5 have been canceled herein without prejudice to further prosecution. Support for the above amendments can be found in Applicants' specification at, for example, page 8, lines 25-30. Thus, no new matter has been added.

In view of the above amendments and the following remarks, Applicants respectfully request reconsideration and allowance of claims 1, 6-10, and 16.

Drawings

The Examiner objected to the drawings, asserting that sequence listings included in the specification are not to be duplicated in the drawings. The Examiner cited 37 C.F.R. §§ 1.58(a) and 1.83 in support of the objection.

Applicants respectfully disagree. As a preliminary matter, 37 C.F.R. § 1.58(a) refers to chemical and mathematical formulae, and has no bearing on the grounds of the Examiner's objection. Further, while 37 C.F.R. § 1.83 states that Sequence Listings included in the

specification are not permitted to be included in the drawings, an exception applies to applications filed under 35 U.S.C. § 371. Applicants respectfully assert that the drawings contain sequences and identifiers, but not a Sequence Listing, which is a separate portion of the application. Moreover, Applicants respectfully assert that since the present application was filed under 35 U.S.C. § 371, the rule against the inclusion of Sequence Listings in the drawings is inapplicable. Accordingly, Applicants respectfully request withdrawal of the objection to the drawings.

Specification

The Examiner noted that trademarks in the specification should be capitalized wherever they appear and accompanied by generic terminology. Applicants have amended pages 12, 21, 26-28, 30, and 34 of the specification herein to capitalize trademarks and to include generic terminology.

In light of the above amendments, Applicants respectfully request withdrawal of the objections to the specification.

Rejections under 35 U.S.C. § 112

The Examiner rejected claims 1-10 and 16 under 35 U.S.C. § 112, first paragraph, as allegedly lacking enablement. The Examiner based the rejection on three grounds. First, the Examiner alleged that Applicants' disclosure "fails to teach how to make and use the peptide of SEQ ID NO:1" and that "the polypeptides comprising structurally and functionally undefined sequences derived from SEQ ID NO:1 are also not enabled . . . ." Second, the Examiner asserted that Applicants' disclosure fails to provide sufficient guidance as to making amino acid substitutions. Finally, the Examiner alleged that Applicants' disclosure fails to provide sufficient guidance as to using the polypeptides encoded by SEQ ID NO:1 and SEQ ID NO:36 for diagnostic purposes.

Applicants' respectfully disagree. Without acquiescing to the Examiner's rejection and to expedite prosecution, however, Applicants have amended independent claim 1 to recite a purified polypeptide comprising an amino acid sequence selected from the group consisting of: (a) the amino acid sequence of SEQ ID NO:1, 3, or 36; (b) a sequence having at least seven

contiguous residues of the amino acid sequence of SEQ ID NO:1; (c) a sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO:1; and (d) a sequence having at least 85% sequence identity to a fragment of SEQ ID NO:1 at least seven contiguous residues in length. Applicants note that the sequences set forth in SEQ ID NO:1 and SEQ ID NO:36 are encompassed in SEQ ID NO:3, and thus are elected subject matter.

The present claims are fully enabled, particularly in light of Applicants' disclosure of methods for making and using BNP nucleic acids and polypeptides. Applicants refer the Examiner to sections of the specification that teach how to construct nucleic acid sequences encoding BNP isoforms (*See*, Applicants' specification at page 8, line 17 to page 9, line 19), how to obtain BNP polypeptides (*See*, Applicants' specification at page 11, line 26 to page 12, line 21), how to use the polypeptides diagnostically and therapeutically (*See*, the Examples 5, 6, and 10), and how to detect polypeptides and nucleic acids (*See*, Applicants' specification at page 20, line 29 to page 29, line 18). A person having ordinary skill in the art at the time of Applicants' priority date would have understood that the methods taught in the Examples (*e.g.*, the cloning of BNP isoforms in Examples 2, 3, and 4; the production of anti-BNP antibodies in Examples 5 and 6; and *in vivo* and *in vitro* uses of synthetic BNP peptides in Examples 8, 9, and 10) with respect to human BNP2, human BNP3, or canine BNP2 polypeptides can be performed for any polypeptide as recited in the present claims.

Applicants' disclosure also provides sufficient guidance with respect to amino acid substitutions and variants of SEQ ID NO:1. Enablement "is not precluded even if some experimentation is necessary." *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367 (Fed. Cir. 1986), cert. denied, 480 U.S. 947 (1987). As stated by the Federal Circuit, "a considerable amount of experimentation is permissible if . . . the specification in question provides a reasonable amount of guidance with respect to the direction in which the experiment should proceed." *In re Wands*, 858 F.2d 731, 737 (Fed. Cir. 1988). Applicants' disclosure satisfies this requirement. For example, Applicants' specification at pages 8-9 teaches polypeptides with "an amino acid sequence of 10, 15, 20, 25, 30, or more residues in length" and a particular sequence identity to SEQ ID NO:1. Applicants' specification also teaches that SEQ ID NO:1 can include the 33 amino acid C-terminal fragment of human BNP2 (*See*, Applicants' specification at page 9, lines 4-6), and teaches how to generate antibodies with specificity for

polypeptides having the sequence set forth in SEQ ID NO:1 (*See*, Applicants' specification at page 23, lines 23-25). Applicants' specification also teaches how to create chimeric natriuretic polypeptides using the N-terminal and C-terminal regions of different natriuretic polypeptides (*See*, the specification at page 12, lines 9-21). For example, Applicants' specification teaches that the C-terminal fragment of human BNP2, set forth in SEQ ID NO:1, can be used in combination with the N-terminus of another natriuretic polypeptide to form chimeric polypeptides with various biological activities. Further, Applicants' specification teaches that polypeptides can have a sequence set forth by a particular formula, and suggests particular amino acid residues for substitutions at different positions (*See*, Applicants' specification at page 12, line 22 to page 13, line 10). In light of these teachings, Applicants respectfully assert that the specification provides sufficient guidance with respect to amino acid substitutions, such that no undue experimentation would have been required for a person having ordinary skill in the art to make and use the recited polypeptides.

Applicants' specification also provides several examples demonstrating how the claimed polypeptides can be used diagnostically. For example, Applicants' specification teaches methods for diagnosing heart conditions, including detecting the presence, absence, or level of BNP2 or BNP3 in a patient's biological sample. (*See*, Applicants' specification at page 4, lines 5-10.) Applicants' specification further teaches that the presence or level of BNP isoforms can be assessed by either measuring BNP2 or BNP3 polypeptides or ribonucleic acids. (*See*, Applicants' specification at page 7, lines 23-24.) A person of ordinary skill in the art at the time of Applicants' priority date would have understood these teachings to apply to each of the polypeptides disclosed in the specification, and to nucleic acids encoding such polypeptides. In addition, Applicants' specification teaches several methods for detecting BNP isoforms and nucleic acid sequences encoding BNP isoforms, methods by which one may use the claimed polypeptides to monitor treatment of a patient "based on a combination of the presence, absence, or level of the BNP isoform and the level of other cardiac markers." (*See*, Applicants' specification at page 20, lines 25-26.) Such methods were well within the level of skill in the art at the time of Applicants' priority date. For at least these reasons, it is clear that no undue experimentation would have been required to make a polypeptide as recited in the present

claims, and to use the polypeptide for diagnosing or monitoring a heart condition in a patient, for example.

In light of the above, it is clear that the present claims are fully enabled. As such, Applicants respectfully request withdrawal of the rejection of claims 1, 6-10, and 16 under 35 U.S.C. § 112, first paragraph.

The Examiner also rejected claims 1-10 and 16 under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the written description requirement. The Examiner asserted that the disclosure fails to disclose sufficient species for the broad genus of the claimed invention and the claims fail to "require any particular biological activity/conserved structure/distinguishing feature." The Examiner also alleged that Applicants' disclosure fails to sufficiently identify a structural and functional relationship for the variants or fragments encompassed by claims 1-10 and 16. The Examiner also alleged that the disclosure fails to identify conserved domains.

Applicants respectfully disagree. Again, Applicants have herein amended claim 1 to recite a purified polypeptide comprising an amino acid sequence selected from the group consisting of: (a) the amino acid sequence of SEQ ID NO:1, 3, or 36; (b) a sequence having at least seven contiguous residues of the amino acid sequence of SEQ ID NO:1; (c) a sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO:1; and (d) a sequence having at least 85% sequence identity to a fragment of SEQ ID NO:1 at least seven contiguous residues in length. Written description is "a question of fact, judged from the perspective of one of ordinary skill in the art as of the relevant filing date." *Falko-Gunter Falkner v. Inglis*, 448 F.3d 1357, 1363 (Fed. Cir. 2006). The test for sufficiency of support in a patent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." *Ralston Purina Co. v. Far-Mar-Co., Inc.*, 772 F.2d 1570, 1575 (Fed. Cir. 1985) (quoting *In re Kaslow*, 707 F.2d 1366, 1375 (Fed. Cir. 1983)). *See also* M.P.E.P. § 2163.02.

Applicants disagree with the Examiner's assertion that the claims encompass a genus of polypeptides that is "defined only by sequence similarity," and submit that the recited polypeptides are defined by more than just sequence similarity. Indeed, Applicants' specification discloses a relationship between functional and structural characteristics of the

recited polypeptides. As taught in Applicants' specification, for example, BNP isoforms "can be used to diagnose heart conditions and monitor treatment of heart conditions." (*See*, Applicants' specification at page 2, lines 16-17; *see also* pages 19-20.) Heart conditions for which the recited polypeptides can be employed include "heart failure, unstable angina, acute myocardial infarction, or hypertension." (*See*, Applicants' specification at page 3, lines 10-11.) Applicants' specification also teaches that the claimed polypeptides can function to stimulate cyclic GMP production, to stimulate vasoactivity, and to increase diuresis or natriuresis. (*See*, Applicants' specification at page 5-6; *see also* Examples 8 and 9, pages 34-35.) A person of ordinary skill in the art reading the specification at the time of Applicants' priority date would have understood the claims to relate to BNP isoforms possessing the recited structures and performing the specified functions, and would have appreciated that Applicants invented and were in possession of the recited polypeptides. Thus, the present claims are adequately described.

In light of the above, Applicants respectfully request withdrawal of the rejections of claims 1, 6-10, and 16 under 35 U.S.C. § 112, first paragraph.

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 1 and 16 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,948,761 (the Sellhamer *et al.* patent). The Examiner also rejected these claims under 35 U.S.C. § 102(b) as anticipated by U.S. Patent No. 5,434,133 (the Tanaka *et al.* patent). The Examiner alleged that the Sellhamer *et al.* patent "teaches an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:48, which meets the limitation as recited in instant claim 1." The Examiner also alleged that the Tanaka *et al.* patent "teaches an isolated polypeptide comprising the amino acid sequence of SEQ ID NO:41, which meets the limitation as recited in instant claim 1."

Applicants respectfully disagree. A claim is anticipated under 35 U.S.C. § 102(b) only if each and every limitation is disclosed in a single prior art reference. *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 639 (Fed. Cir. 1989) and M.P.E.P. § 2131.

Present claim 1 recites a purified polypeptide comprising an amino acid sequence selected from the group consisting of: (a) the amino acid sequence of SEQ ID NO:1, 3, or 36; (b) a sequence having at least seven contiguous residues of the amino acid sequence of SEQ ID

NO:1; (c) a sequence having at least 85% sequence identity to the amino acid sequence of SEQ ID NO:1; and (d) a sequence having at least 85% sequence identity to a fragment of SEQ ID NO:1 at least seven contiguous residues in length. The Sellhamer *et al.* sequence is not "*the* amino acid sequence of SEQ ID NO:1, 3, or 36," as recited in part (a) of present claim 1. Further, SEQ ID NO:48 of the Sellhamer *et al.* patent does not include any portion of SEQ ID NO:1, as required in parts (b), (c), and (d) of present claim 1. Thus, the Sellhamer *et al.* patent fails to disclose each and every limitation of present claims 1 and 16, and therefore cannot anticipate the present claims. Accordingly, Applicants respectfully request withdrawal of this rejection of claims 1 and 16 under 35 U.S.C. § 102(b).

Similarly, SEQ ID NO:41 of the Tanaka *et al.* patent is not "*the* amino acid sequence of SEQ ID NO:1, 3, or 36," as recited in part (a) of present claim 1, nor does it include any portion of SEQ ID NO:1, as required by parts (b), (c), and (d) of present claim 1. Thus, the Tanaka *et al.* patent fails to disclose each and every element of the claims, and therefore cannot anticipate the claims. In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1 and 16 under 35 U.S.C. § 102(b).

The Examiner also rejected claims 1, 3, 5, 7, 9, and 16 under 35 U.S.C. § 102(e) as allegedly being anticipated by U.S. Patent No. 6,812,339 (the Venter *et al.* patent). Specifically, the Examiner asserted that the Venter *et al.* patent teaches a polypeptide of at least 6 contiguous amino acid residues that meets the limitation as recited in instant claim 1. The Examiner also alleged that the Venter *et al.* patent teaches "a composition comprising the claimed polypeptide in a compound or solution for diagnosis, which meets the limitation of a pharmaceutical composition comprising the claimed polypeptide and a pharmaceutically acceptable carrier" as recited in claim 16.

Applicants respectfully disagree. Again, the present claims 1 expressly recite particular structures: that the polypeptides have the amino acid sequence of SEQ ID NO:1, 3, or 36; that the polypeptides have at least seven contiguous residues of the amino acid sequence of SEQ ID NO:1; that the polypeptides have at least 85% sequence identity to the amino acid sequence of SEQ ID NO:1; or that the polypeptides have at least 85% sequence identity to a fragment of SEQ ID NO:1 at least seven contiguous residues in length. SEQ ID NO:7086 of the Venter *et al.*

patent does not have at least 85% sequence identity to a fragment of SEQ ID NO:1 at least seven contiguous residues in length as required by present claim 1. Thus, the Venter *et al.* patent fails to disclose each and every element of the claims and therefore cannot anticipate the claims.

In light of the above, Applicants respectfully request withdrawal of the rejection of claims 1, 3, 5, 7, 9, and 16 under 35 U.S.C. § 102(e).

Information Disclosure Statement

Applicants note that an Information Disclosure Statement (IDS) was filed on August 25, 2006. Applicants respectfully request the Examiner to return an initialed copy of the Form PTO-1449 that accompanied the IDS. A copy of the Form PTO-1449 is attached for the Examiner's convenience.

CONCLUSION

Applicants submit that claims 1, 6-10, and 16 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

Please apply any charges or credits to deposit account 06-1050.

Respectfully submitted,

Date: /January 5, 2009/

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Substitute Form PTO-1449 (Modified) U.S. Department of Commerce Patent and Trademark Office	Attorney's Docket No. 07039-409US1	Application No. 10/561,014
Information Disclosure Statement by Applicant (Use several sheets if necessary) (37 CFR §1.98(b))	Applicant Shuchong Pan et al.	
	Filing Date December 16, 2005	Group Art Unit 1649

U.S. Patent Documents

Examiner Initial	Desig. ID	Document Number	Publication Date	Patentee	Class	Subclass	Filing Date If Appropriate
	1	4,034,074	07/05/77	Miles			
	2	4,098,876	07/04/78	Piasio et al.			
	3	4,233,402	11/11/80	Maggio et al.			
	4	4,996,143	02/26/91	Heller et al.			
	5	5,114,923	05/19/92	Seilhamer et al.			
	6	5,296,347	03/22/94	LaMotte, III			
	7	5,565,322	10/15/96	Heller			
	8	5,580,859	12/03/96	Felgner et al.			
	9	5,583,108	12/10/96	Wei et al.			
	10	5,589,466	12/31/96	Felgner et al.			
	11	5,849,489	12/15/98	Heller			
	12	6,124,430	09/26/00	Mischak et al.			
	13	6,162,603	12/19/00	Heller			
	14	6,376,207	04/23/02	Mischak et al.			

Foreign Patent Documents or Published Foreign Patent Applications

Examiner Initial	Desig. ID	Document Number	Publication Date	Country or Patent Office	Class	Subclass	Translation Yes	Translation No
	15	WO 84/03825	10/11/84	WIPO				
	16	WO 00/71576	11/30/00	WIPO				
	17	WO 01/44284	06/21/01	WIPO				

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
	18	Abdelhafiz, "Heart failure in older people: causes, diagnosis and treatment," Age Ageing, 2002, 31(1):29-36
	19	Best et al., "Dendroaspis natriuretic peptide relaxes isolated human arteries and veins," Cardiovas. Res., 2002, 55:375-384
	20	Burger and Burger, "BNP in decompensated heart failure: Diagnostic, prognostic and therapeutic potential," Curr. Opin. Investig. Drugs, 2001, 2(7):929-35

Examiner Signature	Date Considered

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.

Substitute Form PTO-1449 (Modified) U.S. Department of Commerce Patent and Trademark Office	Attorney's Docket No. 07039-409US1	Application No. 10/561,014
Information Disclosure Statement by Applicant (Use several sheets if necessary)	Applicant Shuchong Pan et al.	
(37 CFR §1.98(b))	Filing Date December 16, 2005	Group Art Unit 1649

Other Documents (include Author, Title, Date, and Place of Publication)

Examiner Initial	Desig. ID	Document
	21	Chaurand et al., "Peptide and Protein Identification by Matrix-Assisted Laser Desorption Ionization (MALDI) and MALDI-Post-Source Decay Time-of-Flight Mass Spectrometry," J. Am. Soc. Mass Spectrom., 1999, 10(2):91-103
	22	Cole et al., "The EBV-Hybridoma Technique and Its Application to Human Lung Cancer," Monoclonal Antibodies and Cancer Therapy, 1985, Alan R. Liss, Inc., pp. 77-96
	23	Cote et al., "Generation of human monoclonal antibodies reactive with cellular antigens," Proc. Natl. Acad. Sci. USA, 1983, 80:2026-2030
	24	Cowie and Mendez, "BNP and Congestive Heart Failure," Prog. Cardiovasc. Dis., 2002, 44(4):293-321
	25	Gevaert et al., "Protein identification based on matrix assisted laser desorption/ionization-post source decay-mass spectrometry," Electrophoresis, 2001, 22(9):1645-51
	26	Guatelli et al., "Isothermal, *in vitro* amplification of nucleic acids by a multienzyme reaction modeled after retroviral replication," Proc. Natl. Acad. Sci. USA, 1990, 87:1874-1878
	27	Huse et al., "Generation of a Large Combinatorial Library of the Immunoglobulin Repertoire in Phage Lambda," Science, 1989, 246:1275-1281
	28	Hyrup and Nielsen, "Peptide Nucleic Acids (PNA): Synthesis, Properties and Potential Applications," Bioorgan. Med. Chem., 1996, 4:5-23
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	34	Sagnella, "Practical implications of current natriuretic peptide research," J. Renin. Angiotensin Aldosterone Syst., 2000, 1(4):304-315
	35	Ausubel et al. (eds.), Short Protocols in Molecular Biology, 1992, Chapters 8 and 11, Green Publishing Associates and John Wiley & Sons
	36	Summerton and Weller, "Morpholino Antisense Oligomers: Design, Preparation, and Properties," Antisense Nucleic Acid Drug Dev., 1997, 7:187-195
	37	Tremblay et al., "Biochemistry and physiology of the natruiretic peptide receiptor guanylyl cyclases," Mol. Cell. Biochem., 2002, 230(1-2):31-47
	38	Walther et al., "Natriuretic peptide system in fetal heart and circulation," J. Hypertens., 2002, 20(5):786-791
	39	Weiss, "Hot Prospect for New Gene Amplifier," Science, 1991, 254:1292-1293

Examiner Signature	Date Considered

EXAMINER: Initials citation considered. Draw line through citation if not in conformance and not considered. Include copy of this form with next communication to applicant.